REMARKS

Status of the Claims

Claims 1-52 are pending in the application. Claims 8-12, 14-20, and 24-49 were withdrawn from consideration due to Restriction and have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the canceled subject matter in a continuation or divisional application. Claims 1, 50, 51 and 52 have been amended. Claim 23 remains withdrawn. Claims 1-5, 21, 22, 23, and 50-52 remain pending.

Support for the amendments to claims 1, 50, 51 and 52 can be found, for example, in Example 12 and in paragraphs 158 and 167 to 186 of the specification. No new matter has been added.

Restriction

Claim 23 recites a method of preparing the pharmaceutical composition of claim 1. Claim 23 (Group XIX) was restricted from the claims of Group I. While the Examiner has made the restriction between Group I and Group XIX final, upon allowance of the elected product claims in Group I, the withdrawn process claims of Group XIX should be considered for rejoinder as outlined in MPEP 821.04(b). Upon rejoinder of claims directed to a previously nonelected process claims, the restriction requirement between the elected product of Group I and rejoined process of Group XIX will be withdrawn.

The Rejection of the Claims for Obviousness-type Double Patenting Should Be Withdrawn

I. Claims 1-7, 13, 21, and 22 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of US Patent No. 5,470,826 (the '826 patent). This rejection is respectfully traversed.

The '826 patent is drawn to polypeptides exhibiting an inhibitory action over follitropin. The patent provides *no information* on formulating or for dosage amounts for the use of the polypeptides. The Examiner continues to dismiss this fact. While a double patenting rejection is based solely on the disclosure of the claims, which in the instant case do not recite any dosage

range, it is also worth nothing that the specification itself is also *completely silent* as to possible dosage ranges. It is therefore submitted that a skilled person would not consider this citation as provide an enabling disclosure of a pharmaceutical composition providing a dosage of follistatin or a fragment(s) or analogue thereof, for the treatment or prevention of a disease associated with fibrosis or any other condition.

Moreover, the dosage rates and formulations are not subject to mere optimization and would not be obvious to a skilled person, especially given the complexity when dealing with patients that have liver disease. See, for example, the attached article titled "Prescribing in Liver Disease", by Pirmohamed, M. (2006) *Medicine* 35:1, pages 31-34. A copy of which is provided in **Appendix A**. This article makes it clear that determining dosage rates for subjects with liver disease is far from straight forward.

The office has the initial burden of establishing a prima *facie case* of obviousness. In light of the comments above, this burden has not been established, and the rejection of the claims should be withdrawn.

II. Claims 1-7, 13, 21, and 22 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 87 of copending Application No. 10/318,283 (the '283 application). This rejection is respectfully traversed.

Claims 1-7, 13, 21, and 22 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 60 of copending Application No. 10/515,049 (the '049 application). This rejection is respectfully traversed.

Claims 1-7, 13, 21, and 22 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51 and 57-60 of copending Application No. 10/571,837 (the '837 application). This rejection is respectfully traversed.

The immediately referenced nonstatutory obviousness-type double patenting rejections are improper. The present application and the '283, '049, and '837 applications are not commonly owned. Thus, the rejections are improper for the following reasons.

The Purposes for a Double Patenting Rejection to Prevent the Unjustified Timewise Extension of the Right to Exclude Granted by a Patent and to Prevent Harassment by Multiple Parties Do Not Apply to the Present Case

Applicants respectfully submit that the present double patenting rejections are improper. MPEP Section 804 indicates that:

> The doctrine of double patenting seeks to prevent the unjustified extension of patent exclusivity of the term of the patent. The public policy behind this doctrine is that:
>
> The public should . . . be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent, but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill in the art and prior art other than the invention claimed in the issued patent.

MPEP (Rev. 5, Aug. 2006), Section 804, page 800-11.

As further noted in the discussion that follows, "double patenting exists when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982)." Clearly, in the present case, the extension of patent term is not an issue. The present application has a filing date of January 12, 2004 and if issued into a patent would expire before the expiration date of a patent issuing from the '283, '049, and '837 applications.

The prohibition against the unjust extension of patent term is further reiterated in Section 804 of the MPEP, page 800-21, which sets forth that a nonstatutory double patenting rejection "is based on a judicially created doctrine grounded in public policy so as to prevent the unjustified or improper timewise extension of the right to exclude granted by a patent. *In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re White*, 405 F.2d 904, 160 USPQ 417 (CCPA 1969); *In re Schneller*, 397

F.2d 350, 158 USPQ 210 (CCPA 1968); *In re Sarett*, 327 F.2d 1005, 140 USPQ 474 (CCPA 1964).

The present application has a filing date that is earlier than the filing dates the '283, '049, and '837 applications. Accordingly there is no unjust patent term extension.

A further rationale for requiring a terminal disclaimer is the concern of possible harassment by multiple assignees. The United States Court of Custom and Appeals in *In re Van Ornum* confirmed that this was a further rationale for requiring a terminal disclaimer and the tying together of the ownership (non-alienation) of two patents (686 F.2d 937, 948, 214 U.S.P.Q 761, 770 (CCPA 1982).

Whenever the courts have discussed the concern of harassment by multiple assignees it has always been in terms of commonly owned patents that might subsequently be assigned or transferred to different parties. The court addressed this common ownership in *In re Van Ornum,* where it stated that "[t]his provision would prevent harassment of an alleged infringer by multiple parties due to **subsequent** different ownership of multiple patents granted as the result of filing a terminal disclaimer to overcome a double patenting rejection" (686 F.2d at 945, 214 U.S.P.Q at 768; emphasis added). In *Chisom,* a discussion of the issue of harassment by multiple assignees states that "[e]ven though both patents are issued to the same patentee or assignee, it is possible that ownership of the two would be divided by later transfer and assignments" (Chapter 9, section 9.04[2][b][ii]; emphasis added). Since a terminal disclaimer can only be filed where the patents or applications are commonly owned, the requirement that a terminal disclaimer include a non-alienation clause dictates that there is common ownership.

With regard to the '283, '049, and '837 applications and the application at issue, these inventions were never commonly owned and the inventors in each case were by law required to assign to different owners (employers). At no time were these two inventions commonly owned. Accordingly, appellants respectfully submit that the issue of harassment by multiple assignees does not apply to this case.

There Is No Double Patenting Issue for the Present Application in View of the '283, '049, and '837 applications

The section of the MPEP that governs the present situation is MPEP 804.03 IV, pages 800-37 through 800-39, regarding rejections under 35 USC 102 and 103 and double patenting. Form paragraph *7.21.01 Provisional Rejection, 35 USC 103(a), Common Assignee or at Least One Common Inventor* should be applied to the present situation. The present application and the '283, '049, and '837 applications do not have a common assignee or are not subject to a joint research agreement as defined by The CREATE Act. The present application and the '283, '049, and '837 applications do share a common inventor.

MPEP form paragraph 7.21.01 indicates that in the present case the claims of the '283, '049, and '837 applications should be provisionally rejected under 35 USC 103(a) as obvious over the present application, which is copending. As stated in the form paragraph, "[b]ased upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application." MPEP, page 800-38.

As noted in the discussion that follows, this form paragraph should be used by an examiner to provisionally reject claims not patentably distinct from the disclosure in a copending application having an earlier U.S. filing date and also having either a common assignee or at least one common inventor. As noted on page 800-39, "if an application has a later effective U.S. filing date than a conflicting issued patent, the examiner should consider making a rejection in the application, based on the patent, under 35 U.S.C. 102(e) or 102(e)/103(a) using form paragraph 7.15.02 or 7.21.02. The discussion distinguishes the present situation from the situation where the application and the patent are subject to a joint research agreement under The CREATE Act.

The fact overlooked by the Examiner in the present application is the fact that the **present application has an effective filing date that is earlier** than the filing date of the '283, '049, and '837 applications. Thus, the '283, '049, and '837 applications are not prior art for

purposes of double patenting under 35 U.S.C. 102 or 103. The present application is the earlier filed application.

In conclusion, based upon the procedures set forth in the MPEP based upon current patent law there is no double patenting issue for the present application in view of the '283, '049, and '837 applications. Accordingly, the double patenting rejections should be withdrawn.

The CREATE Act Safe-Harbor Provisions Do Not Apply to the Present Application

As noted above, the present application and the '283, '049, and '837 applications are not commonly assigned, nor subject to a joint research agreement, as provided by The CREATE Act. Thus, the double patenting concerns brought about by the CREATE Act are not an issue in the present application. The CREATE Act provides a simple means of extending the "safe harbor" provisions of current law that treats inventions of a common owner similarly to inventions made by a single person. To promote collaborative research within organizations, Congress enacted the Patent Law Amendments of 1984, which, inter alia, exempt "common owner" inventors from the application of certain types of prior art and information in obviousness determinations, subject to the exercise of the same double patenting principles that apply when inventions are made by a single inventor. Importantly, "[p]atents issued under this Act shall be enforceable in the same manner, to the same extent, and for the same term as when patents are issued to a common owner or are subject to common assignment. The doctrine of "obviousness-type double patenting," a judicial doctrine used by courts to prevent patentees from obtaining an unjustifiable extension of the amount of time to exercise a patent's right to exclude, shall apply to such patent." H.R. REP. 108-425, page 5.

As set forth in Department of Commerce RIN 0651-AB76:

> Once an examiner has established a *prima facie* case of obviousness under 35 U.S.C. 103(a), the burden is on the applicant to overcome the rejection by invoking 35 U.S.C. 103(c) as amended by the CREATE Act. . . To overcome such a rejection via the CREATE Act, the applicant must provide a statement in compliance with §1.104(c)(4) to the effect that the prior art and the claimed invention were made by or on the behalf of parties to a joint research agreement, within the meaning of 35 U.S.C. 103(c)(3), which was in effect on or before the date the claimed invention was made, and that the claimed invention was made as

> a result of activities undertaken within the scope of the joint research agreement. . . If the applicant disqualifies the subject matter relied upon by the examiner in accordance with the CREATE Act and the procedures set forth in this final rule, the examiner will treat the application under examination and the 35 U.S.C. 102(e), (f), or (g) prior art as if they are commonly owned for purposes of 35 U.S.C. 103.

Federal Register Vol. 70, No. 177, 54259, 54261.

Thus, parties who seek to benefit from the CREATE Act waive the right to enforce any patent separately from any earlier patent that would otherwise have formed the basis for an obviousness-type double patenting rejection. A double patenting rejection is authorized where an applicant invokes the new provisions of 35 U.S.C. 103(c), even though there is neither a common inventor nor a common patent owner. Rule 1.109(b).

As discussed in the MPEP and in the CREATE Act, double patenting rejections may arise as a result of the amendment to 35 U.S.C. 103(c) by the CREATE Act (Pub. L. 108-453, 118 Stat. 3596 (2004)). Congress recognized that this amendment to 35 U.S.C. 103(c) would result in situations in which there would be double patenting rejections between applications not owned by the same party (see, H.R. Rep No. 108-425, at 5,6 (2003). For purposes of double patenting analysis, the application or patent and the subject matter disqualified under 35 U.S.C. 103(c) as amended by the CREATE Act will be treated as if commonly owned.

> Congress recognized that this amendment to 35 U.S.C. 103(c) would result in situations in which there would be double patenting between applications not owned by the same party. *See* H.R. Rep. No. 108-425, at 5-6 (2003). Therefore, the Office is providing the following guidelines for double patenting rejections based upon a patent or application that is not commonly owned but was disqualified under 35 U.S.C. 103(c) as resulting from activities undertaken within the scope of a joint research agreement, which will be incorporated into the next revision of the MPEP.

Federal Register Vol. 70, No. 177, 54259, 54261.

However, this new category of double patenting created by the CREATE Act does not apply to the present application. Applicants are not seeking to benefit from the provisions provided by the CREATE Act. Furthermore, Applicants cannot take advantage of the provisions

of the CREATE Act since there was no joint research agreement in place between the assignee of the present application and the assignee of the '283, '049, and '837 applications. Accordingly, double-patenting under the CREATE Act does not apply to the present application and the rejection should be withdrawn.

Applicants further note that the MPEP section addressing the requirements of a double patenting rejection states that an "[o]bviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a ***commonly owned patent***, or a ***non-commonly owned patent but subject to a joint research agreement*** as set forth in 35 U.S.C. 103(c)(2) and (3), when the issuance of a second patent would provide ***unjustified extension of the term*** of the right to exclude granted by a patent." MPEP § 804(II)(B)(1) (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USPQ2d 1869 (Fed. Cir. 2001) and *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000)) (emphasis added). The present application and the '283, '049, and '837 applications are not commonly owned, nor are they subject to a joint research agreement. Further, there is no unjustified extension of term in this case. Thus, the fundamental purpose for which the judicially created doctrine of obviousness-type double patenting was intended, i.e., to prevent the unjustified extension of the term of the right to exclude granted by a patent (which purpose is repeated throughout the MPEP), is not present in this case (*See,* MPEP § 804, § 804 (II), § 804(II)(B) and § 804(II)(B)(1)).

Additionally, the MPEP states:

> If the provisions of 35 U.S.C. 103(c)(1) apply to the commonly owned conflicting inventions of different inventive entities or if the provisions of 35 U.S.C. 103(c)(2) apply to non-commonly owned inventions subject to a joint research agreement and thereby obviate the obviousness rejection(s), double patenting rejection(s) should be made (or maintained) as appropriate. **If, however, it is determined that the provisions of 35 U.S.C. 103(c) do NOT apply** because the inventions were not commonly owned or subject to an obligation of assignment to the same person at the time the later invention was made, or because the claimed invention did NOT result from activities undertaken within the scope of a joint research agreement as required by 35 U.S.C. 103(c)(2) and (3), **and** there is evidence of record to indicate that a patent or application is prior art against the application being examined, the examiner should make (A) any appropriate double patenting rejection(s), and (B) the appropriate prior art

> rejection(s) under 35 U.S.C. 102 and/or 35 U.S.C. 103 in the application being examined.

MPEP § 804.03(IV) (emphasis added). Again, none of these fact patterns identified as appropriate for a double patenting rejection are found in the instant case. The provisions of §103(c) do not apply and the '283, '049, and '837 applications are not prior art against the present application.

Thus, Applicants respectfully submit that the requirements for a proper double patenting rejection as set forth in the MPEP are not met in this case, and therefore, the present double patenting rejection is improper.

For all these reasons, the rejection of the claims on the ground of non-statutory obviousness-type double patenting over the '283, '049, and '837 applications should be withdrawn.

Even if the rejections were proper, the Examiner should allow the earlier filed application to issue

The above obviousness-type double patenting rejections are improper and should be withdrawn. These are *provisional* rejections because the alleged conflicting claims have not issued as part of a patent. Applicants respectfully note that the present application has an earlier effective U.S. filing date than the '283, '049, and '837 applications. At which time allowable subject has been agreed upon, and the provisional nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the earlier filed of the pending applications, the Examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. See, MPEP 804.

The Examiner is further requested to reconsider the double patenting rejection related to U.S. Application No. 10/318,283. Claim 87 of the '283 application is drawn to a composition comprising activin or an activinβC inhibitory molecule. The instant claims have been amended to recite a composition comprising follistatin. The office has the initial burden of establishing a

prima facie case of double patenting. This requirement has not be satisfied. Claim 87 of the '283 application is drawn to a completely different composition than the instant claims and neither suggest or teach a composition comprising follistatin. A *prima facie* case of double patenting has not been established, and the rejection should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 6, 7, and 13 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite. Claims 6, 7 and 13 have been canceled, and the rejection of the claims is moot.

The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

I. Claims 1, 2, 4-6, 13, 21, and 50-52 were rejected under 35 U.S.C. §103(a) as being obvious in view of WO01/05998 and in view of WO 99/10364. These rejections are respectfully traversed.

Both WO01/05998 and WO99/10364 discuss methods of use for follistatin-3. Firstly, it is submitted that follistatin-3 is a follistatin-related protein [FSTL3], also known as FST-related protein [FSRP] (and does have a sequence as shown in SEQ ID NO: 2), which is different in its physical, chemical and physiological properties to follistatin. The encoding gene is also known as FST-related gene [FLRG]. Claims 1, 2, 4-6, 13, 21, AND 50-52 as currently amended recite specific pharmaceutical compositions employing follistatin or fragments or analogues thereof.

Establishing a *prima facie* case of obviousness requires assessment of the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), which provides the framework for applying the statutory language of § 103. Under the "Graham Factors," the Examiner is required to:

1. Determine the scope and content of the prior art;
2. Ascertain the differences between the prior art and the claims at issue;
3. Resolve the level of ordinary skill in the pertinent art; and
4. Consider any relevant secondary considerations.

Furthermore, a *prima facie* case of obviousness under 35 U.S.C. § 103(a) requires that the combination of references places the claimed subject matter in the public domain prior to

Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obvious requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references and that a reasonable expectation of success exists in such a combination. In the instant case, neither of the cited references discloses, explicitly or implicitly, a pharmaceutical composition comprising a dosage form comprising 0.001mg to 5mg of follistatin, as recited in the claims. The disclosures of WO01/05998 and WO99/10364 simply cannot be combined to arrive at the claimed methods.

The Examiner is respectfully requested to consider the following facts that demonstrate the *vast structural and functional* differences between follistatin and FSTL3.

The proteins, FSTL3 and follistatin, are encoded by separate genes. Although they do show some homology, each is a unique protein which has its own distinct roles as demonstrated when the gene for each protein is knocked out [see Matzuk *et al*, (1995) *Nature* 374:360 (provided in **Appendix B**) for follistatin knock-out & Mukherjee *et al* (2007) *Proc Natl Acad Sci USA* 104:1348 (provided in **Appendix C**)] and distinct actions.

Although the two proteins have three follistatin domains with some homology, follistatin-3 and follistatin share only 61.5% amino acid sequence similarity and 43.25% identity. Domain 1 in follistatin contains a heparin binding site that enables follistatin to bind to heparan sulphate proteoglycans on cell surfaces. In contrast to follistatin, FSTL-3 has a different domain 1 that lacks a heparin binding site and is unable to bind to cell surfaces. In a detailed study of the actions of follistatin and FSTL-3, Sidis *et al* (2006) *Endocrinology* 147: 3586-3597 (provide here with in **Appendix D**) made the following comments regarding the biological activity of the two proteins (Page 3587*):*

> *"FSTL-3 does not have an heparin binding site, cannot bind to cell surface proteoglycans and is a weak antagonist of endogenous [autocrine] activin despite being only slightly less potent in neutralizing exogenous [endocrine/paracrine] activin. These distinctions between FSTL-3 and follistatin support the concept that the presence of a functional heparin binding site is a critical biochemical determinant for endogenous activin inhibition."*

On page 3595 they state as a conclusion to their studies:

> *"In summary, our results clarify the activin-binding affinity among the follistatin isoforms and FSTL-3 and demonstrate that their differential activin regulating activity is dependent on their relative cell-surface-binding activity rather than on differential activin-binding affinity. Our results also define the relative specificity of binding and inhibitory activity for a number of related TGF-β-family ligands by the follistatin isoforms and FSTL-3, with FSTL-3 being almost completely inactive in regulating BMP ligands, thereby suggesting that in vivo, FSTL-3 is unlikely to regulate BMP activity. Finally, our results suggest that the in vivo biological roles of the FST isoforms and FSTL-3 are likely to be distinct, dependent on their relative cell-surface binding activity and consequent compartmentalisation within the body as well as on colocalization of biosynthesis in different tissues."*

These differences are highlighted by the different outcomes when their genes are subjected to targeted disruption. Matzuk *et al* (1995) (Appendix B), report that knock-out of the follistatin gene results in death of all offspring within a few hours after birth due to an inability to breathe, and the pups have abnormal skin as well as whisker and skeletal abnormalities. In contrast, disruption of the FSTL3 gene is reported by Mukherjee *et al*. (2007) (Appendix C), to show that the mice survive to adulthood, have enlarged islets of Langerhans in the pancreas, reduced visceral fat and enhanced glucose tolerance and increased insulin sensitivity. They also develop hypertension. Thus, it is clear that FSTL-3 and Follistatin are not equivalent compounds.

In addition, as implied above, although follistatin binds activins A, B and AB, which may be involved in fibrotic events, it should be noted that follistatin can also bind a number of other members of the TGFß superfamily, but with lesser affinity, such as Growth and Differentiation Factor (GDF) 9, bone morphogenetic protein (BMP) 2, BMP4, BMP6 ,BMP7 and BMP15 (see Lin S-Y, Morrison JR, Phillips DJ, de Kretser DM. (2003) "Regulation of ovarian function by the TGFß superfamily and follistatin" *Reproduction* 126:133-148). While the capacity of follistatin to neutralize the actions of myostatin has been studied extensively, recent data suggest that follistatin can also block some actions of the BMPs mentioned (Abe Y, Abe T, Aida Y, Hara Y, Maeda K (2004) "Follistatin restricts bone morphogenetic protein (BMP)-2 action on the differentiation of osteoblasts in fetal rat mandibular cells" *J Bone Miner Res* 19:1302-1307;

Glister C, Kemp CF, Knight PG (2004) "Bone morphogenetic protein (BMP) ligands and receptors in bovine ovarian follicle cells: actions of BMP-4,-6 and-7 on granulosa cells and differential modulation of Smad-1 phosphorylation by follistatin" *Reproduction* 127:239-254; Otsuka F, Moore RK, Iemura S-i, Ueno N, Shimasaki S (2001) "Follistatin inhibits the function of the oocyte-derived factor BMP-15" *Biochem Biophys Res Commun* 289:961-966).

Furthermore, conditions associated with fibrosis are typically accompanied or preceded by inflammation causing cell death by necrosis. This complex process requires the involvement of many cell types both within the tissue or organ concerned, but also involves the invasion of the damaged tissue by components of blood-borne cells such as leucocytes, together with exposure to a variety of compounds that form part of the organism's inflammatory response e.g. many cytokines that are produced in a highly coordinated manner.

Consequently, it is submitted that the prophetic uses of follistatin-3 espoused in documents WO 99/10364 and WO 01/05998, or the doses to be used in such uses could not be predicted by a skilled person at the date of those documents, as the uses are speculative, being unsupported by *in vivo* experimental data, or even experimental data relating to treatment of conditions associated with fibrosis (or any other condition).

Thus, it is submitted that a skilled person, on reading either of these documents, would not have considered using follistatin in place of follistatin-3, would not have considered the use of follistatin-3 for treatment of any condition, including conditions associated with fibrosis, and would not have been provided with any useful information towards dosing of follistatin, or even follistatin-3.

It is therefore submitted that the claims are not obvious in view of either, or both of documents WO 99/10364 and WO 01/05998, and the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Furthermore, although the U.S. Supreme Court recently declined to permit a "rigid" application of the teaching-suggestion-motivation to combine (TSM) test to obviousness determinations, the Court did hold that the presence or absence of a teaching, suggestion, or motivation to combine the cited references provides a "helpful insight" regarding the obviousness of an invention. *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385 (U.S. 2007). The

Supreme Court went on to acknowledge the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in way the claimed invention does" in an obvious determination. *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007; citing *KSR Int'l Co. v. Teleflex, Inc.*; emphasis added). While in the instant case the cited references simply cannot be modified to produce the claimed invention as neither teaches the composition of use comprising follistatin, the Examiner has also provided only broad conclusory statements and has failed to identify a sufficient reason for one of skill in the art to combine the references to arrive at the claimed invention. Therefore, no *reason* to combine the cited references exists, and even if combined, the combination would not render the claimed invention obvious for the reasons set forth above.

II. Claims 1, 2, 3, 5, 13, 21, 22, and 50-52 were rejected under 35 U.S.C. §103(a) as being obvious in view of U.S. Patent No. 5,041,538 (the '538 patent). This rejection is respectfully traversed.

The '538 patent discloses the isolation of porcine follistatin 315 and 288, and the prophetic use of these molecules for decreasing fertility/spermatogenesis in female/male mammals (column 10, lines 1-14), with a suggested dosage of from about 0.1 to about 1 milligrams per Kg. of body weight for administration on a regular basis as a male contraceptive (column 12, lines 16-21).

As submitted previously, the prophetic therapeutic uses and suggested dosage rates are not supported by any *in vivo* or even *in vitro* studies, and therefore the comments above (in relation to documents WO 99/10364 and WO 01/05998) are equally applicable here. It is therefore submitted that a skilled person would not consider this citation to provide an enabling disclosure of a pharmaceutical composition providing a dosage of follistatin or a fragment(s) or analogue thereof, for the treatment or prevention of a disease associated with fibrosis or any other condition.

In addition, while the suggested dose range of from about 0.1 to about 1 milligrams per Kg. of body weight for administration on a regular basis as a male contraceptive may have been

a best guess in the context of fertility regulation, it is submitted that this is far too high a dosage rate for the use of follistatin to regulate fibrosis. In addition, the use of a lower dose provides a commercial advantage.

The claims have been amended to recite a pharmaceutical compositions wherein the compositions are provided as dosage forms comprising from 0.001mg to 5mg of follistatin (or narrower ranges). Even at the lowest dosage rate considered by the '538 patent (0.1mg/kg body weight), an average person of from 60-75kg would require at least 6 to 7.5mg.

We also submit that dosage rates and formulations are not subject to mere optimization and would not be obvious to a skilled person, especially given the complexity when dealing with patients that have liver disease. See, for example, the attached article titled "Prescribing in Liver Disease", by Pirmohamed, M. (2006) *Medicine* **35**:1, pages 31-34 (provided in **Appendix A**). This article makes it clear that determining dosage rates for subjects with liver disease is far from straight forward.

Thus, in view of the Graham factors discussed above, *a prima facie* case of obviousness has not been established and the rejection of the claims should be withdrawn.

CONCLUSIONS

The Examiner is respectfully requested to withdraw the rejections and allow claims 1-5, 21, 22, and 50-52. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments were not made earlier because the applicant earnestly believes the specification is non-obvious for the breadth of the claims as previously amended.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/kelly j. williamson/

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